REMARKS

Entry of the foregoing, reexamination and further and favorable reconsideration of the subject application in light of the following remarks, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested.

By the foregoing amendment, claims 10-20 and 25-31 have been canceled without prejudice or disclaimer of the subject matter recited therein. Further, claims 32-56 have been added. Support for new claims 32-56 can be found throughout the specification and in the originally filed claims. Specifically, support for claim 32 can be found in canceled claim 10. Support for claim 33 can be found in canceled claim 12. Support for claim 34 can be found in canceled claim 13. Support for claim 35 can be found in canceled claim 14. Support for claim 36 can be found in canceled claim 15. Support for claim 37 can be found in canceled claim 16. Support for claim 38 can be found in canceled claim 17. Support for claim 39 can be found in canceled claim 11. Support for claim 40 can be found in canceled claim 25. Support for claim 41 can be found in canceled claim 26. Support for claim 42 can be found in canceled claim 18. Support for claim 43 can be found on page 14, lines 34-37 of the specification and in the originally filed claim 21. Support for claim 44 can be found in canceled claim 10. Support for claim 45 can be found in canceled claim 27. Support for claim 46 can be found in canceled claim 28. Support for claim 47 can be found in canceled claim 29. Support for claim 48 can be found in canceled claim 18. Support for claim 49 can be found in Example I. Support for claim 50 can be found on page 19, lines 3-12 of the specification. Support for claim 51 can be found on page 18, line

28 through page 19 line 2 of the specification. Support for claim 52 can be found on page 14, lines 34-37 of the specification and in originally filed claim 21. Support for claims 53 and 55 can be found on page 14, line 38 through page 15, line 10 of the specification as well as in Example 6 and in originally filed claim 22. Further, support for claims 54 and 56 can be found on page 14, line 38 through page 5, line 10 of the specification and in originally filed claim 22. Accordingly, no new matter has been added.

Turning now to the Official Action, each of the issues raised by the Examiner will be discussed in detail below.

I. Double Patenting Rejection

Claims 10-20 and 25-31 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-9, 23 and 24 of copending Application Serial No. 09/043,933. While acknowledging that the conflicting claims are not identical, the Examiner has stated that the claims are not patentably distinct from each other because the vaccinia vector(s) in the present application has identical polypeptides to the parent application. This rejection is respectfully traversed.

It is noted that this provisional obviousness-type double patenting rejection is rendered moot in light of the cancellation of claims 10-20 and 25-31. However, to the extent that this rejection may apply to new claims 32-56, Applicants submit that claims of the present application are directed to a composition essentially containing one or more

recombinant vector(s) for the expression of the specified papillomavirus polypeptides whereas claims 1-9, 23 and 24 of Application Serial No. 09/043,933 recite a composition essentially containing one or more of the specified papillomavirus polypeptides.

Therefore, the "nucleic acids based" composition of the present invention is patentably distinct from, and not an obvious variation of, the "polypeptides based" composition of the co-pending patent Application Serial No. 09/043,933.

Since the presently claimed invention is not an obvious variation of the invention defined in the claims of the identified co-pending application, there is no basis for the provisional non-statutory obviousness-type double patenting rejection. Accordingly, applicants respectfully request withdrawal of the double patenting rejection.

II. Rejections Under 35 U.S.C. § 112, second paragraph

Claims 10-20 and 25-30 have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. Applicants respectfully traverse this rejection.

Claims 10, 25, 26 and 30 are allegedly indefinite for referring to polypeptides from the early (E6 and/or E7) "region" and the late (L1 and/or L2) "region" of a human papilloma virus. This portion of the rejection is rendered moot in light of the cancellation of claims 10-20 and 25-31. However, to the extent that this rejection may apply to claims 32-56, applicants off the following arguments

The Examiner has stated that the specification does not set forth clear metes and

bounds of the intended early and late "regions" of the papillomavirus. Applicants respectfully disagree. The term "region" with respect to early and late regions of the papilloma virus is well known in the art and this term is clearly defined in the introduction of the present application. Page 1, lines 14-18 of the specification, states that the HPV genome "comprises an early and a late region. The late region contains two reading frames L1 and L2 which code for the major components of the capsid. The early region contains at least the reading frames El, E2, E4, E5, E6 and E7." (Emphasis added.)

Thus, "region" clearly refers to specific part of the HPV genome characterized in that they "contain open reading frames." Moreover, the term "region" is routinely used and perfectly understandable by the skilled person in the genetic field, especially in the papillomavirus domain. See for example p. 860, first paragraph, of the Background Chapter of Hines et al. (cited by the Examiner).

To expedite prosecution in the subject application, and not to acquiesce to the Examiner's rejection, applicants no longer refer in the new claims to "regions" but instead to a DNA sequence encoding an early or late polypeptide (for example, see new claim 32). This language is used throughout the specification (for example, on page 4, lines 29-30, pages 12-13). The phrase "polypeptide from the early region" is synonymous with "early polypeptide," and the phrase "polypeptide from the late region" is synonymous with "late polypeptide". Both terms are certainly well understood by those skilled in the art and are interchangeable.

Claims 10 and 15-19 are allegedly indefinite for reciting the term "fragments." This

portion of the rejection is rendered moot in light of the cancellation of claims 10-20 and 25-31. However, to the extent that this rejection may apply to claims 32-56, applicants offer the following arguments.

The Examiner has stated that there is insufficient description to adequately describe the metes and bounds of any DNA "fragment" that could possibly be "derived" from undefined "regions" of the papilloma virus. As indicated on page 8, lines 9-10 of the specification, the term "fragment" refers to a DNA sequence or DNA gene encoding a papillomavirus polypeptide, and the term "polypeptide" is defined on page 4, lines 8-26 of the specification. In order to expedite prosecution in the subject application and not acquiesce to the Examiner's rejection, applicants have used the term"sequence" instead of "fragment" in the new claims.

Claims 11-14, 16, 18, 19, 26 and 28-30 are allegedly indefinite for reciting the term "derived" as the Examiner is not clear as to what the term "derived" means. This portion of the rejection is rendered moot in light of the cancellation of claims 10-20 and 25-31. However, to the extent that this rejection may apply to claims 32-56, applicants provide the following arguments.

With respect to recitation of the term "derived" in connection with the papillomavirus polypeptide in claims 11 and 26, applicants draw the Examiner's attention to page 4, lines 8-26 of the specification, which states that the term "derived" refers to a native, a chimeric or a variant papillomavirus polypeptide. Additionally, the working examples of the present application plainly illustrate the use of a recombinant vector

expressing native papillomavirus polypeptides as well as variant papillomavirus polypeptides with the internal residues responsible for the oncogenic phenotype deleted (an E6 variant having amino acids 111-115 deleted as compared to the native E6 polypeptide and an E7 variant having amino acids 21-26 deleted as compared to the native E7 polypeptide). It is noted, however, to expedite prosecution in the subject application and not acquiesce to the Examiner's rejection, applicants do not recite the term "derived" in new claims 32-56.

With respect to the recitation of the term "derived" in connection with the recombinant vector or with the immunostimulatory polypeptide in claims 12-14, 16-19 and 28-30, respectively, the Examiner's attention is drawn to the fact that the corresponding new claims do not recite the term "derived." However, applicants submit that the term "derived" in connection with the immunostimulatory polypeptide is defined on page 5, lines 29-34 of the specification, where it is indicated that, in the context of the present invention, it is possible to use a native immunostimulatory polypeptide or a portion, a chimeric or a mutant (or variant) thereof. Further, the term "derived" in connection with the recombinant vector is defined on page 8, line 25 to page 9, line 34 and on page 11, lines 11-31 of the specification, where it is described how a recombinant vector can be obtained from a virus genome in the context of the present invention:

> A preferred recombinant vector within the frame-work of the invention is a viral vector into whose genome there have been inserted the above-mentioned DNA fragments so as to allow their transfer and their expression in a host cell or such vectors, as well as the techniques for preparing them, are known to person skilled in the art.

Claims 12 and 27 are allegedly indefinite for not reciting a proper Markush group. This portion of the rejection is rendered moot in light of the cancellation of claims 10-20 and 25-31. However, to the extent that this rejection may apply to claims 32-56, it is respectfully traversed. New claims 33 and 45, which correspond to canceled claims 12 and 27, respectively, recite proper Markush language.

Claim 17 (now new claim 38) is allegedly indefinite for reciting "zones" of the vaccinia virus since the Examiner is not clear as to the meaning of this term. This portion of the rejection is rendered moot in light of the cancellation of claims 10-20 and 25-31. However, to the extent that this rejection may apply to claims 32-56, applicants provide the following arguments.

Applicants submit that the phase "excision zones" is clearly defined in the specification on page 11, lines 25-31. The term "excision zones" refers to the deletions that have been mapped in the genome of the MVA virus as compared to the wild type Ankara vaccinia virus genome. See Meyer et al. (*J. Gen. Virol.*, 72:1031-8, 1991, cited on page 11, lines 29-30 of the specification). Meyer et al. identifies the six deletion or excision regions present in the MVA genome. However, in order to expedite prosecution in the subject application and not acquiesce to the Examiner's rejection, applicants have used the term "region" in new claim 85 as opposed to the term "zone".

Claim 20 is allegedly indefinite for referring to a vector that is "alive or killed" because, according to the Examiner, viruses, and not vectors, can be killed or attenuated. This portion of the rejection is rendered moot in light of the cancellation of claims 10-20

and 25-31. However, to the extent that this rejection may apply to claims 32-56, applicants also respectfully traverse such rejection, particularly since new claims 32-56 do not recite the phrase "alive or killed."

Claim 25 is allegedly indefinite for reciting the term "variant." This portion of the rejection is rendered moot in light of the cancellation of claims 10-20 and 25-31. However, to the extent that this rejection may apply to claims 32-56, applicants offer the following arguments.

The term "variant" in claim 25 refers to the non-oncogenic E6 and/or E7 polypeptides which are disclosed on page 4, line 37 to page 5, line 6 of the specification. However, in order to expedite prosecution in the subject application and not acquiesce to the Examiner's rejection, new claims 32-56 do not recite the term "variant."

In view of all the remarks provided above with regard to the 35 U.S.C. § 112, second paragraph rejection, withdrawal of such rejection is respectfully requested.

III. Rejections Under 35 U.S.C. § 112, first paragraph

Claims 10-19, 25, 26, 28, 29 and 30 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the invention was filed, had possession of the claimed invention. This rejection is respectfully traversed.

It is noted that this rejection is rendered moot in light of the cancellation of claims 10-20 and 25-31. Moreover, this rejection is not applicable to new claims 32-56 since, to

expedite prosecution in the subject application and not acquiesce to the Examiner's rejection, new claims 32-56 do not recite the terms "fragments," "derived" or "variants."

Therefore, applicants respectfully request withdrawal of the 35 U.S.C. § 112, first paragraph.

IV. Rejections Under 35 U.S.C. § 102(b)

Claims 10-13, 18, 23-27, 30 and 31 have been rejected under 35 U.S.C. § 102(b) as allgedly being anticipated by Stanley et al. in WO 96/29091. This rejection respectfully traversed.

It is noted that this rejection has been rendered moot in light of the cancellation of claims 10-20 and 25-31. However, to the extent that this rejection may apply to claims 32-56, applicants submit the following arguments.

Stanley et al. (WO 96/29091) was published on September 26, 1996, which is less than one year prior to the effective U.S. filing date of July 29, 1997 for the present application. Therefore, Stanley et al. cannot be properly used as prior art under 35 U.S.C. § 102(b). Additionally, the present application properly claims benefit of priority to French application number 96 09584 filed on July 30, 1996, which was prior to the publication date of WO 96/29091. The Examiner has acknowledged the claim for foreign priority as well as receipt of the certified copy of the priority document on the front of the Office Action Summary. Thus, Stanley et al. is also not an applicable reference under 35 U.S.C. § 102(a).

The Examiner's attention is drawn to the fact that a patent search using the

inventor's name revealed an issued U.S. patent (U.S. Patent No. 6,096,869, a copy of which is submitted with the concurrently filed Information Disclosure Statement) covering what appears to be the same invention as WO 96/29091. This patent granted on August 1, 2000 has a U.S. filing date of March 22, 1995 (the same filing date of Stanley et al.). However, since the '869 Stanley et al. patent fails to teach every element of the claimed invention, it cannot anticipate the currently pending claims.

The '869 Stanley et al. patent found that "IL-12 is present in 100% of regressing HPV-induced tumours . . . unlike many other cytokines also surveyed." See column 2, lines 48-51 of the '869 Stanley et al. patent. Based on this observation, the '869 Stanley et al. patent proposed a treatment involving IL-12, or its inducer (*i.e.*, IL-12 encoding nucleic acid) as a fundamental and compulsory active element (column 3, lines 20-21, column 4, line 62 and throughout the '869 Stanley et al. patent). This treatment is illustrated by administering a "pharmaceutical composition" comprising said IL-12 (column 3, lines 33-39).

According to an embodiment, said composition can further comprise additional components (column 3, lines 40-41). More specifically the '869 Stanley et al. patent states at column 3, line 47 to column 4, line 3 that said composition can comprise two separate components:

(i) the IL-12 or encoding nucleic acid (basis of their invention) and

(ii) "a papillomavirus antigen, or a vector encoding and able to cause expression of a papillomavirus antigen".

Please note, the singular used in the phrase "a papillomavirus antigen . . . ."

It is then specified that said compound (ii), (i.e. a papillomavirus antigen, or a vector encoding and able to cause expression of a papillomavirus antigen) can comprise "at least one papillomavirus protein or antigenic fragment or fusion protein" or alternatively "**a vector** which can comprise **at least one** recombinant vaccinia virus encoding a polypeptide with at least a substantial part of the sequence of **at least one** papillomavirus protein El, E2, E4, E5, E6, E7, Ll and/or L2" (end of column 3, lines 66-67 column 4). The key elements of the '869 Stanley et al. patent composition are as follows: In one embodiment, the pharmaceutical composition comprises IL-12 **and a** vector encoding for and able to cause expression of **a** papillomavirus antigen. Said encoded polypeptide (i.e. an antigen) has at least a substantial part of the sequence of **at least one** papillomavirus protein El, E2, E4, E5, E6, E7, LI and/or L2. This can be interpreted as meaning that while there is ONLY ONE encoded antigen (i.e., **a** antigen), said antigen can comprise one or more of the listed proteins. Thus, as there is only one antigen when there is more than one listed protein, the skilled artisan can interpret this as meaning that said antigen is a fusion protein of many proteins. This limited interpretation of the teachings of the '869 Stanley et al. patent is further confirmed by the experimental data providing examples where **only one** protein E7 OR E6 is administered in accordance with the invention. No examples with vectors are provided. See column 14. This interpretation is further in accordance with the allowed claims which recite the combination of (i) IL-12 and (ii) a nucleic acid molecule encoding **a protein** consisting essentially of at least one antigenic portion of a

papillomavirus protein wherein said protein is selected from the group consisting of E6, E7, L1 and L2 (claim 5).

Additionally, the disclosure of the '869 Stanley et al. patent is limited to the fact that IL-12 p40 is expressed in 100% of regressing HPV-induced lesions analyzed in the preliminary study leading to the disclosed invention. Moreover, the transcription status of a series of cytokines, including IL-2, in cervical tissues obtained from normal women (Table E) or from HPV-infected patients with either regressing (Table D) or non regressing (Tables A, B and C) lesions were studied.

From the experimental data summarized in Tables A-C, it can be concluded that all normal tissues do not express IL-12 p40 (Table E) as well as the majority of non-regressing lesions (Tables A and B), whereas IL-12 p40 expression was observed in all regressing tumors (Table D). The appearance of IL-12 p40 transcripts in the non-regressing lesions grouped in Table C was believed to indicate a possibility that the patients, from whom these samples were taken, were in very early stage of regression but at a time when clinical improvement was not yet measurable (column 13, lines 51-56).

With respect to IL-2 expression, normal cervix showed transcripts for IL-2 (Table E), as well as the majority of the regressing genital lesions (4/5 in Table D). IL-2 expression is also observed in some of the non-regressing lesions (5/8 in Table C, 2/7 in Table B and 0/8 in Table A). Thus, the pattern of IL-2 expression is quite different of the pattern observed for IL-12 p40 in the different categories of cervical biopsies analyzed in this study.

It is noted that no other cytokine shows a similar expression pattern as the one obtained for IL-12 T 40 (specifically expressed in the regressing lesions and absent in normal tissues and non-regressing lesions). Therefore, the disclosure of the '869 Stanley et al. patent could in no way be broadened to the use of a recombinant vector encoding a non-IL-12 immunostimulatory molecule.

The main conceptual difference between the '869 Stanley et al. patent and the present invention resides in the fact that according to the present invention the presence of either IL-12 or any cytokine is not compulsory. While the '869 Stanley et al. patent is mainly based on supposed IL-12 properties, the present invention involves special antigen combinations, or combination of the corresponding encoding genes, (i.e., combination of polypeptides encoded by the early region of papillomavirus and of polypeptides encoded by the late region of papillomavirus) with improved properties when compared to the HPV prior art teachings.

Claim 32 is drawn to a combination of DNA sequences leading to the expression of both early and late polypeptides under non-fused form. The presence of DNA sequences coding for both the early and late polypeptide is clearly disclosed. The non-fused form is provided by the phrase ". . . said DNA sequences being placed under the control of the elements necessary for their expression in a host cell or organism." This allows the DNA sequence(s) encoding an early polypeptide and the DNA sequence(s) encoding a late polypeptide to be distinctively expressed and therefore cannot lead to the expression of any fusion protein. Accordingly, the present claims are drawn to the separate coexpression of

early and late polypeptides. Claims 44 and 45 refer to the above-claimed object further combined with DNA sequences encoding at least one immunostimulatory polypeptide, for example IL-12.

In view of the above, applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 102(b) and submit that an anticipation rejection under any other sectionof 35 U.S.C. § 102 is not proper.

V. Rejections Under 35 U.S.C. § 103 (a)

Claims 10-16, 18-20 and 23-31 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Stanely et al. in view of Boursnell et al. in (WO 92/16636), Galloway, Hines et al. and Gajewski. This rejection is respectfully traversed. It is noted that this rejection is rendered moot in light of the cancellation of claims 10-20 and 25-31. However, to the extent that this rejection may apply to claim 32-56, applicants offer the following arguments.

In proceedings before the Patent and Trademark Office, the Examiner bears the burden of establishing a *prima facie* case of obviousness based upon the prior art. The Examiner can satisfy this burden by showing, first, that the cited prior art coupled with the general knowledge at the time of the invention must contain some suggestion or incentive to motivate a skilled artisan to modify or combine references. *See In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988); *In re Skinner*, 2 U.S.P.Q.2d 1788, 1790 (Bd. Pat. App. & Int. 1986). Second, the Examiner must show that the modification or combination of prior art references must have a reasonable expectation of success (at the

time of the invention). *See Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1209, 18 U.S.P.Q.2d 1016, 1023 (Fed. Cir. 1991). Lastly, the Examiner must show that the cited or combined references teach each and every limitation of the claims. *See In re Zurko*, 111 F.3d 887, 888- 89, 42 U.S.P.Q.2d 1476, 1478 (Fed. Cir. 1997); *In re Wilson*, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970). As will be described in detail below, the Examiner has not satisfied any of these three burdens.

The remarks above regarding Stanley et al. are incorporated herein by reference.

Boursnell et al. (WO 92/16636) teaches a recombinant virus expressing wild type or variants of the early polypeptides of both HPV-16 and HPV-18 for use as an immunotherapeutic vaccine to treat the conditions caused by an HPV infection. To reduce the likelihood of recombinant events, the homologous early sequences from HPV-16 and HPV-18 are arranged in an inverted orientation with respect to one another. Boursnell et al. further discloses an embodiment where the corresponding E7 (or E6) polypeptide from HPV-16 and the E7 (or E6) polypeptide from HPV-18 are fused together to form a single open reading frame. The later is illustrated in working examples using a vaccinia virus of Wyeth strain. Following intranasal inoculation into mice, the recombinant vaccinia virus is detected in lungs indicating that it retains its ability to replicate in the host organism. For therapeutic use, Boursnell et al. proposes to apply to the arm of a patient virus droplets which are then scarified with a bifurcated needle.

As acknowledged by the Examiner, Boursnell et al. does not teach nor suggest a vector based composition further encoding a late papillomavirus polypeptide and/or an

polypeptide having an immunostimulatory activity.

Galloway discloses that it should be feasible to develop prophylactic vaccines to prevent HPV infection using the LI and L2 capsid proteins or therapeutic vaccines to modulate the development or recurrence of disease based on the E6 and El oncoproteins or other viral proteins. See abstract, page 187.

Please note that this general teaching is summarized in the "state of the art" presented in the present application (page 2, lines 20-27), although based on other documents (EP 462187 for the prophylactic approach, i.e. using late proteins; and WO 93/02184 for the therapeutic approach, i.e. using early proteins).

The Examiner refers to Galloway's indication that most individuals have antibodies that recognize the capsid proteins, especially L2. However, the prevalence of antibodies against some HPV proteins is not representative of the disease state as it is further explained in Galloway who adds that "several groups have demonstrated that the prevalence of antibodies to the HPV-16 or -18 E7 protein is increased in cases with cervical cancer compared with age-matched controls" (page 189 first paragraph, second column). It has been shown that infected individuals have type-specific antibodies to a conformational epitope on the LI protein and that these antibodies correlate strongly with a history of disease (page 189 second paragraph, second column)." Thus, the fact that HPV proteins induce a humoral (antibody-based) immune response in patients does in no way correlate with a protective antitumoral effect.

Galloway merely reviews the experimental assays performed in animal models with

papillomavirus polypeptides (no mention to vector based compositions is made), more specifically Galloway refers to (i) prophylactic vaccinations relying on late papillomavirus polypeptides (page 190 second column) and (ii) independent therapeutic vaccinations relying on early polypeptides (p 191 first paragraph, first column).

Galloway never discloses nor suggests the combination of both approaches. At most, Galloway refers to a vaccine that comprises both the L2 and E7 polypeptides (disclaimed in the claimed invention) under the form of a fusion protein (with carrier molecules). See the sentence overlapping end of page 190 and bottom of page 191 of Galloway.

This "L2+E7" based vaccine is detailed in WO 93/00436 (Jarrett et al.) and WO 94/23037 (Campo et al.). More specifically, said L2 and E7 polypeptides of BPV-4 have been produced by the recombinant route in *E. coli* as GST or β-gal fusion proteins. An antitumoral protection of immunoprophylactic type is observed in calves vaccinated with the mixture of purified GST-L2 + GST-E7 polypeptides before the viral challenge (Figure 4 and Example 2 of WO 93/00436, Experiment # 4 of Table 2, page 21 and Figure 3B of WO 94/23037). When comparing Figures 3 and 4 of WO 93/00436 and Figures 3B and 3C of WO 94/23037, one would conclude that vaccination with either L2- or "L2+E7" results in the same prophylactic protective effect. In other words, E7 is inefficient in this context. Moreover, in spite of the presence of E7 early polypeptide, the L2+E7 vaccine does not confer any protection against tumors pre-existing before the vaccination (therapeutic effect), as indicated in WO 93/00436 page 15, last paragraph and in WO 94/23037 page 21, lines

22-25.

Additionally, analysis of the immunological activity of such fusion E7 or L2 proteins performed in WO 91/23037 (Campo et al., see Table J., page 12) provides evidence that the immunological activity observed in animals treated with the fusion protein (e.g., β-gal- E7 or GST-L2, respectively) results in an immune response to both the early or late polypeptide, respectively, and the carrier β-gal or GST, respectively (see column noted β-gal-E7 or GST-L2). With this respect, please refer to the results presented in Table I:

-first line (i.e., Animal treated with β-gal-E7), columns noted β-gal (shows reaction to β-gal only), GST-E7 (shows reaction to E7 only) and β-gal E7(shows reaction to both β-gal and E7);

-second line (i.e., Animal treated with GST-L2), columns noted GST (shows reaction to GST only), β-gal-L2 (shows reaction to L2 only) and GST-L2 (shows reaction to both GST and L2).

Finally, none of the recited documents (Galloway, WO 93/00436 or WO 94/23037) mentions nor suggests the combined use of papilloma polypeptides and immunostimulatory molecule in order to enhance the protective effect of the former. Hence, the combination of references as set forth by the Examiner fail to teach each and every limitation of the currently pending claims.

Hines et al. reports that the injection of E7-derived peptides into mice protected the mice from tumor formation after challenge with HPV-transformed tumor cells. Hines et al.

proposes a "cellular adoptive protocol" to accelerate anti-tumoral response. This protocol involves the *ex vivo* stimulation of peripheral blood lymphocytes obtained from a patient suffering from cancer with HPV oncoprotein peptides (to render the patient's lymphocytes responsive to HPV) in the presence of IL-2.

Applicants draw the Examiner's attention on the fact that IL-2 is necessary for lymphocyte activation to convert lymphocytes to cytotoxic T lymphocytes. Thus, IL-2 here is not used to enhance anti-HPV immunity but rather to provide activation of naive lymphocytes and make them acquire a cytotoxic phenotype. Hines et al. also report immunoprophylactic data obtained with VLPs (this is a L1 and/or L2 polypeptide based composition not a viral vector based one).

Hines et al. does not teach a composition combining DNA sequences encoding early and late papillomavirus polypeptides as claimed in the present invention. Further, Hines et al. does not teach any association with an immunostimulatory molecule encoding sequence.

Moreover, Hines et al. does not refer to a method of treatment (see new claims 53-56 of the present application) comprising administration of a composition of the claimed invention (Hines et al. performs the *ex vivo* protocol).

Gajewski teaches the function of B7.1 as a cofactor for *in vivo* IL-2 synthesis and proposes the use of B7.1 to direct the production of IL-2 necessary in the proliferation and activation of lymphocytes into cytotoxic T lymphocytes. However, Gajewski does not teach the co-expression of B7.1 with papilloma polypeptides, nor compositions permitting said coexpression of B7.1 with papillomavirus polypeptides to enhance the anti-

papillomavirus immune response.

All together, the documents cited by the Examiner disclose:

1. a composition comprising one or more early papilloma polypeptides (Boursnell et al., Galloway and Hines et al.);
2. a composition comprising one or more late papilloma polypeptides or VLPs (Galloway and Hines et al.);
3. a composition comprising late L2 papilloma polypeptide and the E7 papilloma polypeptide (Galloway, W093/00436 and W094/23037) (in the form of fusion protein with a carrier); and
4. a composition comprising IL-12 and "a vector encoding and able to cause expression of a papillomavirus antigen" (Stanley et al.).

Therefore, the state of the art discloses either antitumoral compositions relying on early papillomavirus polypeptides or a recombinant vector encoding the early polypeptide (composition 1) or compositions relying on late papillomavirus, polypeptides or a recombinant vector encoding the late polypeptides (composition 2). The state of the art does not motivate one skilled in the art to combine both types of polypeptides.

Even if one of skill in the art were to combine the references as suggested by the Examiner, there would not have been a reasonable expectation of success. At the date the invention was made, the skilled artisan was aware of the results from the composition described above and given the number 3 showing that administration of either L-2 or "L2+E7" results in the same prophylactic protective effect meaning that E7 is inefficient.

Accordingly, the skilled artisan would certainly not have been motivated to prepare a composition combining early and late encoding DNA sequences in order to prepare a composition that co-expresses said early and late polypeptides (different of E7/L2) useful for treating papillomavirus tumors and infection.

Additionally, the skilled artisan would not be motivated to further co-express immunostimulatory compounds, even after reading Stanley et al. for the reason stated above.

Furthermore, it is emphasized that the specific combination of DNA sequences encoding "L2+E7" has been excluded from the currently pending claims. This exclusion is justified on the basis of the recent data reporting the inefficiency of compositions comprising fused L2 and E7 polypeptides in the treatment of papillomavirus infections (see attached Press Release, Exhibit A).

With respect to the presence of an immunostimulatory molecule, none of the cited references teaches the action of said molecule to enhance the protective effect conferred by the papilloma polypeptides. Hines et al. and Gajewski disclose that IL-2 or its cofactor B7.1 can be used to induce the proliferation of naive lymphocytes obtained from a patient and activate their cytotoxic phenotype.

Since in view of the above it is clear that a proper *prima facie* case of obviousness has not been established, applicants respectfully request withdrawal of the 35 U.S.C. § 103(a) rejection.

Claim 17 has been rejected under 35 U.S.C. § 103(a) as being unpatentable over

Stanley et al., Boursnell et al., Galloway, Hines et al. and Gajewski further in view of Meyer et al. This rejection is also respectfully traversed.

The remarks above regarding Stanley et al., Boursnell et al., Galloway, Hines et al. al., and Gajewski are incorporated herein by reference.

Meyer et al. fails to remedy the serious deficiencies of the combination of the primary references. As mentioned page 11, lines 28-31 and page 22, line 33 to page 23, line 3 of the present application, Meyer et al. establishes the mapping of the six deletions (excision zones) that have occurred in the MVA genome during the attenuation process. The sequence of the papillomavirus polypeptides used in the context of the present invention have been introduced within the deletions II and III (see page 23, lines 3-9 of the present application).

However, the present invention is not based on the site of integration of the papillomavirus/immunostimulatory sequences within the
MVA genome, but rather in the specific combinations of papillomavirus sequences and optionally immunostimulatory sequences. Since the combination of references fails to teach or suggest the presently claimed invention, a proper *prima facie* case of obviousness has not been established.

Therefore, applicants respectfully request withdrawal of the 35 U.S.C. § 103(a) rejection.

In view of the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order. Such action is earnestly solicited.

In the event that there are any questions relating to this application, it would be appreciated if the Examiner would telephone the undersigned attorney concerning such questions so that prosecution of this application may be expedited.

Respectfully submitted,

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Date: March 12, 2001

TH-GW Human Papillomavirus Vaccine Development Halted by Cantab and SKB.

Date : 20001000

Sous-titre :

Development for Cantab Pharmaceuticals Plc's TH-GW genital wart vaccine has been ceased due to lack of success in Phase II trials.

Source article :

Antiviral Agents Bulletin; Volume: 13; Issue: 10; Page: N/A; October 2000; ISSN: 0897 9871; United States.

Société : CANTAB PHARMACEUTICALS PLC; SMITHKLINE BEECHAM BIOLOGICALS; <SMITHKLINE BEECHAM PLC>

Résumé :

Cantab Pharmaceuticals plc (Cambridge, U.K.) and its development collaborator, SmithKline Beecham Biologicals (SKB; Rixensart, Belgium), have announced discontinuation of development of Cantab's TH-GW immunotherapeutic human papillomavirus (HPV) vaccine for treatment of genital warts after the vaccine failed to show efficacy in the first of two Phase II trials. TH-GW is a subunit fusion protein vaccine formulated from two fused HPV-6 proteins (L2 and E7) expressed in E. coli along with a proprietary adjuvant (SBAS2 from SKB) to increase T lymphocyte response. The SBAS2 adjuvant is based on the combination of monophosphoryl lipid A (MPL), a detoxified form of Lipid A lipopolysaccharide purified from Salmonella minnesota R595 bacteria, from Corixa Corp. (originally Ribi ImmunoChem), combined with QS21 (QS-21), a purified fraction of saponin extracted from Quillaja saponaria, from Aquila Biopharmaceuticals, Inc. (originally Cambridge Biotech Corp.), plus a proprietary oil-in-water emulsion. The original agreement between Cantab and SKB for development of TH-GW was reported in the July 1996 Bulletin (p. 170). An earlier Phase IIa trial had shown the vaccine to have promise for treatment of genital warts, as reported in the December 1996 Bulletin (p. 324). In the recently completed Phase II trial, no significant difference in the recurrence rate for genital warts was observed at six months between patients receiving TH-GW and a placebo. The trial had enrolled genital warts patients having failed other therapies. The stock price of Cantab in the U.K and U.S. (NASDAQ) declined about 60% shortly after the announcement. However, Cantab has other HPV vaccines in development. TA-CIN is currently in Phase I trials for treatment of cervical dysplasia (as discussed in the July Bulletin, p. 202). TA-CIN is a recombinant HPV type 16 fusion protein which has shown encouraging therapeutic and prophylactic effects in animal models. TA-HPV is in Phase II trials for treatment of cervical

cancer. TA-HPV uses a recombinant vaccinia virus vector for intracellular expression of HPV E6 and E7 antigens which stimulate cytotoxic T lymphocyte (CTL) immunity. This vaccine has shown indications of efficacy as reported in the December 1997 Bulletin (p. 364). Other products in development by Cantab include a DISC HSV vaccine. As reported in the August Bulletin (p. 229), Cantab recently regained rights to this vaccine for prophylactic use from Glaxo Wellcome plc as a result of Glaxo Wellcome's upcoming merger with SKB.

THIS IS A LEAD PARAGRAPH; FULL TEXT IS AVAILABLE IN FORMATS 'LONG' & 'ALL'.

Texte :

Cantab Pharmaceuticals plc (Cambridge, U.K.) and its development collaborator, SmithKline Beecham Biologicals (SKB; Rixensart, Belgium), have announced discontinuation of development of Cantab's TH-GW immunotherapeutic human papillomavirus (HPV) vaccine for treatment of genital warts after the vaccine failed to show efficacy in the first of two Phase II trials. TH-GW is a subunit fusion protein vaccine formulated from two fused HPV-6 proteins (L2 and E7) expressed in E. coli along with a proprietary adjuvant (SBAS2 from SKB) to increase T lymphocyte response. The SBAS2 adjuvant is based on the combination of monophosphoryl lipid A (MPL), a detoxified form of Lipid A lipopolysaccharide purified from Salmonella minnesota R595 bacteria, from Corixa Corp. (originally Ribi ImmunoChem), combined with QS21 (QS-21), a purified fraction of saponin extracted from Quillaja saponaria, from Aquila Biopharmaceuticals, Inc. (originally Cambridge Biotech Corp.), plus a proprietary oil-in-water emulsion. The original agreement between Cantab and SKB for development of TH-GW was reported in the July 1996 Bulletin (p. 170). An earlier Phase IIa trial had shown the vaccine to have promise for treatment of genital warts, as reported in the December 1996 Bulletin (p. 324). In the recently completed Phase II trial, no significant difference in the recurrence rate for genital warts was observed at six months between patients receiving TH-GW and a placebo. The trial had enrolled genital warts patients having failed other therapies. The stock price of Cantab in the U.K and U.S. (NASDAQ) declined about 60% shortly after the announcement. However, Cantab has other HPV vaccines in development. TA-CIN is currently in Phase I trials for treatment of cervical dysplasia (as discussed in the July Bulletin, p. 202). TA-CIN is a recombinant HPV type 16 fusion protein which has shown encouraging therapeutic and prophylactic effects in animal models. TA-HPV is in Phase II trials for treatment of cervical cancer. TA-HPV uses a recombinant vaccinia virus vector for intracellular expression of HPV E6 and E7 antigens which stimulate cytotoxic T lymphocyte (CTL) immunity. This vaccine has shown indications of efficacy as reported in the December 1997 Bulletin (p. 364). Other products in development by Cantab include a DISC HSV vaccine. As reported in the August Bulletin (p. 229), Cantab recently regained rights to this vaccine for prophylactic use from Glaxo Wellcome plc as a result of Glaxo Wellcome's upcoming merger with SKB.

THIS IS THE FULLTEXT.